REMARKS/ARGUMENTS

Upon entry of the instant amendment, claims 19-24 will be canceled without prejudice or disclaimer of the subject matter recited therein, claim 42 will be added, and claims 13, 15, 16 and 27-41 will be amended, whereby claims 13-18 and 25-42 will be pending. Claims 13, 25, 27, 33, 39 and 42 are independent claims. It is noted that claim 40 was previously indicated to be an independent claims, but is, in fact, a dependent claim.

Reconsideration and allowance of the application are respectfully requested.

Response To Rejection Under 35 U.S.C. 112, Second Paragraph

In response to the rejection of claims 13-41 under 35 U.S.C. 112, second paragraph, as being indefinite, Applicants respectfully submit the following.

Applicants respectfully submit that the claimed terminology is readily understandable to one having ordinary skill in the art, whereby the metes and bounds of the claimed subject matter is of a clear scope. However, in order to advance prosecution of the application, Applicants have amended the claims herein to include language that the Examiner considers to be preferable. Therefore, each occurrence of "derivative" terminology has been changed to "compound" terminology. Moreover, "salt thereof" has been changed in each occurrence to "pharmaceutically acceptable salt thereof".

Accordingly, this ground of rejection should be withdrawn.

Response To Rejection Under 35 U.S.C. 112, First Paragraph

Claims 13-15, 17, 18, 25 and 26 are rejected because of the assertion that the specification, while being enabling for the treatment of Alzheimer's disease, does not reasonably provide enablement for the treatment of other neurological diseases that are allegedly related to tau protein. The rejection asserts that the specification does not enable any person skilled in the art to which it pertains, or with it is most nearly connected, to use the invention commensurate in scope with the claims.

In particular, the rejection asserts that for diseases such as Parkinsonisms, Down syndrome, and ischemic cerebrovascular accidents, the state of the art only provides speculations, and no evidence relating them to "tau protein". The rejection contends that the specification mainly relates "tau protein" to the production of "amyloid" which is related to Alzheimer's, but not to other neurological diseases such as Parkinsonisms, Down syndrome, and ischemic cerebrovascular accidents. The rejection asserts that there is no evidence that "amyloid" causes Parkinsonisms, Down syndrome, and ischemic cerebrovascular accidents.

In response, Applicants once again direct the Examiner's attention to the "Background Art" section of Applicants' specification, and the articles cited therein which establish that Applicants' invention is enabled for the therapeutic treatment of diseases such as Parkinsonisms, Down syndrome, and ischemic cerebrovascular accidents. **In particular, as can be seen from a review of the information cited in the originally filed specification, one having ordinary skill in the art would be capable of practicing Applicants' disclosed and claimed invention without undue experimentation.**

In particular, and as discussed in Applicants' specification, beginning on page 1, Applicants have established a sufficient relationship between various conditions and diseases to enable one having ordinary skill in the art to practice their invention without undue experimentation. While these arguments have been presented in Applicants' previous response, they are being resubmitted and emphasized herein.

Initially, Applicants note that the specification with respect to Alzheimer disease discloses that it is known that the degree of appearance of two characteristic pathological changes of Alzheimer disease correlates well to the degree of intellectual dysfunction. It is disclosed that it has been shown, referencing Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985), that senile plaques accumulate extracellularly, and amyloid βprotein has been elucidated as main components (abbreviated as "Aβ"). Moreover, it is disclosed that in the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF") accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component, referencing Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988).

Moreover, it is disclosed that, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of Aβ, referring to Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997). It is disclosed that from these results, it is considered

that, in Alzheimer disease, Aβ abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is disclosed that it is expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents, referring to Sai-shin Igaku [Latest Medicine], 49, 1506 (1994). Thus, the specification points to a relationship with respect to ischemic cerebrovascular accidents.

Still further, it is disclosed that it has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP") as a precursor of Aβ (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it is disclosed that it has been strongly suggested that the accumulation of Aβ is involved in cellular death due to ischemic cerebrovascular disorders. It is also disclosed that other diseases in which abnormal accumulation and agglomeration of Aβ are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, it is disclosed that as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso

[Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

Applicants' respectfully submit that the above provides sufficient basis for one having ordinary skill in the art to practice Applicants' invention without undue experimentation.

Still further, with respect to tau protein, it is disclosed that the tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It is disclosed that it has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). Ii is also disclosed that an enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1"), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3β, FEBS Lett., 325, 167 (1993)).

It is further disclosed that it has been reported that Aβ, the main component of senile

plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by Aβ treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by Aβ treatment and the cell death by Aβ was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, Applicants respectfully submit that their disclosure enables the use of compounds which inhibit the TPK1 activity to suppress the neurotoxicity of Aβ and the formation of PHF enabled to be used as a medicament for therapeutic treatment of Parkinsonisms, Down syndrome, and ischemic cerebrovascular accidents.

Applicants note that the rejection once again does not provide detailed remarks about the enablement and guidance provided in Applicants' originally filed disclosure, but instead points to the assertion that Down syndrome is related to the extra chromosome, and that "parkisonism" has been associated with dopamine or plague formed by cholesterol. Moreover, the rejection asserts that these diseases do not share the same symptoms with Alzheimer's disease since the late stage of Alzheimer's disease tends to have violent episodes whereas the other diseases do not. It is not seen how this assertion in the rejection counters the relationships included in Applicants' originally filed specification. Whether or not one disease may have different symptoms is not germane to whether Applicants' invention is enabled.

Moreover, the rejection references that various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. However, this theory pertains to Aβ causing cell death, and does not change the fact that Applicants have provided sufficient guidance, especially pointing to documentary evidence in the originally filed application, to support the claimed invention.

For the sake of brevity, Applicants are not repeating all of their previously presented arguments relating to the case law and the Examiner's burden. However, Applicants note that in view of the above and their previous arguments, Applicants respectfully submit that the claims are enabled, and the enablement rejection should be withdrawn.

Claims 19-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement and as not being enabled. These grounds of rejection contend that claim 19 is directed to a "method for prophylactic treatment" which does not have a description in terms of the timing of administration or the duration of such a "prophylactic treatment". Moreover, the rejection asserts that because it is not clear what the procedure is for a "method for prophylactic treatment", one skilled in the art cannot practice the claimed method without under experimentation.

In response and in an attempt to advance prosecution of the application, Applicants have canceled claims 19-24. However, the cancellation of these claims is made without agreement or acquiescence with the rejection. For example, Applicants respectfully submit that Applicants' claims comply with the written description and enablement requirements of the patent statutes. For example, attention is directed to the bottom of page 67 through the top of page 68 of the

specification. In particular, in contrast to the assertion in the lack of written description assertion, this portion of the specification does provide a description in terms of the timing and administration, and should be considered to be enabling in the absence of sound technical arguments in the rejection. Regarding duration of the treatment, that one having ordinary skill in the art would continue treatment in a prophylactic manner over a period of time.

In view of the above, Applicants respectfully submit that the rejections of record should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow all the pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions or wishes to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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